

On page 7, at line 11, please amend the paragraph beginning "Figure 11." as follows:

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--Figure 11. Nucleotide sequences of the oligonucleotides (DSABL-1 (SEQ IS NO: 33), DSABL-1c (SEQ IS NO: 34), MSAL-CDR1-1 (SEQ IS NO: 35), MSAL-CDR1-1c (SEQ IS NO: 36), HMVL1 (SEQ IS NO: 37), HMVL2 (SEQ IS NO: 38), HMVL3 (SEQ IS NO: 39), HMVL5 (SEQ IS NO: 40), HMVL8 (SEQ IS NO: 41), HMVL9 (SEQ IS NO: 42), HMVL10 (SEQ IS NO: 43), HMVL6 (SEQ IS NO: 44), HMVL4 (SEQ IS NO: 45), and HMVL7 (SEQ IS NO: 46)) used to construct the MSA1 and MSALVAC-1 variable regions.--

On page 7, at line 13, please amend the paragraph beginning "Figures 12A-C." as follows:

B3
--Figures 12A-C. (A) Nucleotide sequence for the MSA-63 epitope (SEQ ID NO: 19). (B) Amino acid sequence of the MSA-63 epitope encoded by the nucleotide sequence of Figure 12A (SEQ ID NO: 20). (C) MSA-63 oligonucleotides used to construct a modified variable region. Each oligo overlaps for five codons and transitions the entire sequence of Figure 12A (MSA1 (SEQ ID NO: 21), MSA2 (SEQ ID NO: 22), MSA3 (SEQ ID NO: 23), MSA4 (SEQ ID NO: 24), MSA5 (SEQ ID NO: 25), MSA6 (SEQ ID NO: 26), MSA7 (SEQ ID NO: 27)).--

On page 7, at line 17, please amend the paragraph beginning "Figures 13A-C." as follows:

B4
--Figures 13 A-C. (A) Nucleotide sequence for the SP-10 epitope (SEQ ID NO: 9). (B) Amino acid sequence of the SP-10 epitope encoded by the nucleotide sequence of Figure 13A (SEQ ID NO: 10). (C) Oligonucleotides of Sp-10 used to construct a modified variable region (SP1 (SEQ ID NO:11), SP2 (SEQ ID NO:12), SP3 (SEQ ID NO:13), SP4 (SEQ ID NO:15), SP5 (SEQ ID NO:17), and SP6 (SEQ ID NO:18)). SP3a (SEQ ID NO:14) and SP4a (SEQ ID NO:16) are modified to change the codons encoding certain cysteine residues to codons encoding alanine residues.--

On page 7, at line 22, please amend the paragraph beginning "Figure 14." as follows:

--Figure 14. Oligonucleotides of LDH-C4 epitope sequence for construction of a modified variable region gene containing a LDH-C₄ (LDH1 (SEQ ID NO: 47), and LDH2 (SEQ ID NO: 48).--

B5

On page 7, at line 24, please amend the paragraph beginning "Figure 15." as follows:

--Figure 15. Nucleotide (SEQ ID NO: 71) and amino acid (SEQ ID NO: 72) sequences of the consensus contraceptive light chain variable region. --

B6

On page 7, at line 26, please amend the paragraph beginning "Figure 16 A-B." as follows:

--Figures 16 A-B. (A) Sequences of oligos used in the construction of 2CAVHCOL1 (VHC1 (SEQ ID NO: 49), VHC2 (SEQ ID NO: 50), VHC3 (SEQ ID NO: 51), VHC4 (SEQ ID NO: 52), VHC5 (SEQ ID NO: 53), VHC6 (SEQ ID NO: 54), VHC7 (SEQ ID NO: 55), VHC8 (SEQ ID NO: 56), VHC9 (SEQ ID NO: 57), and VHC10 (SEQ ID NO: 58)). (B) Sequences of oligos used in the construction of 2CAVLCOL1 (VLC1 (SEQ ID NO: 59), VLC2 (SEQ ID NO: 60), VLC3 (SEQ ID NO: 61), VLC4 (SEQ ID NO: 62), VLC5 (SEQ ID NO: 63), VLC6 (SEQ ID NO: 64), VLC7 (SEQ ID NO: 65), VLC8 (SEQ ID NO: 66), VLC9 (SEQ ID NO: 67), VLC10 (SEQ ID NO: 68), VLC11 (SEQ ID NO: 69), and VLC12 (SEQ ID NO: 70)).--

B7

On page 38, at line 3, please amend the paragraph beginning "In order to confirm" as follows:

--In order to confirm correct gene sequences of the engineered variable region genes and to eliminate the possibility of unwanted mutations generated during the construction procedure, DNA sequencing was performed using M13/pUC reverse primer (5'AACAGCTATGACCATG 3' (SEQ ID NO:1)) for the clones as well as PCR gene products using 5' end 20 base primer (5' GAATT CATGGCTTG

B8

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GGTGTG 3' (SEQ ID NO: 2)) on automated ABI 377 DNA Sequencer. All clones were confirmed to contain correct sequences.--

On page 40, at line 23, please amend the table beginning "Table 6." as follows:

Table 6. Biotin-Labeled Peptides Derived from CDR Sequences of Mab 31.1

Peptide ID Sequence

- COL311 L1 biotin-N-Thr-Ala-Lys-Ala-Ser-Gln-Ser-Val-Ser-Asn-Asp-Val-Ala
(SEQ ID NO: 3)
- COL311 L2 biotin-N-Ile-Tyr-Tyr-Ala-Ser-Asn-Arg-Tyr-Thr (SEQ ID NO: 4)
- COL311 L3 biotin-N-Phe-Ala-Gln-Gln-Asp-Tyr-Ser-Ser-Pro-Leu-Thr (SEQ ID NO: 5)
- COL311 H1 biotin-N-Phe-Thr-Asn-Tyr-Gly-Met-Asn (SEQ ID NO: 6)
- COL311 H2 biotin-N-Ala-Gly-Trp-Ile-Asn-Thr-Tyr-Thr-Gly-Glu-Pro-Thr-Tyr-Ala-Asp-Asp-Phe-Lys-Gly (SEQ ID NO: 7)
- COL311 H3 biotin-N-Ala-Arg-Ala-Tyr-Tyr-Gly-Lys-Tyr-Phe-Asp-Tyr (SEQ ID NO: 8)

B9

On page 41, at line 25, please amend the paragraph beginning "The nucleotide and protein sequences" as follows:

--The nucleotide and protein sequences of the SP-10 epitope are:

B10

GAA TTC CAG CCT TCA GGT GAA CAT GGC TCC GGT GAA CAG CCT TCT
GGT GAG CAG GCC TCG GGT GAA CAG CCT TCA GGT GAG CAC GCT TCA
GGG GAA CAG GCT TCA GGT GCA CCA ATT TCA AGC ACA TCT ACA GGC
ACA ATA TTA AAT TGC TAC ACA TGT GCT TAT ATG AAT GAT CAA GGA
AAA TGT CTT CGT GGA GAG GGA ACC TGC ATC ACT CAG AAT TC (SEQ ID NO: 9);

Gln Pro Ser Gly Glu His Gly Glu Gln Pro Ser Gly Glu Gln Ala Ser Gly Glu Gln Pro
Ser gly Glu His Ala Ser Gly Glu Gln Ala Ser Gly Ala Gln Ile Ser Ser Thr Ser Thr Gly

B10
Cont.

Thr Ile Leu Asn Cys Tyr Thr Cys Ala Tyr Met Asn Asp Gln Gly Lys Cys Leu Arg Gly
Glu Gly Thr Cys Ile Thr Gln Asn (SEQ ID NO: 10).--

Beginning on page 41, at line 33, continuing to page 42, line 20, please amend the paragraph beginning "The replacement of an antibody's CDR" as follows:

--The replacement of an antibody's CDR with another epitope is made easier by the fact that the variable region sequence of antibodies are relatively short, and are known. One is then able to synthetically generate a series of complementary oligonucleotides that, when annealed and ligated, reconstruct the entire coding region of variable region portion of the gene. In this manner, the CDR is replaced with sequences of the epitope of interest, in this example, SP-10. The following is a list of the sequences of the oligonucleotides designed for cloning SP-10 epitopes into the CDR:

Oligo SP 1 (SEQ ID NO: 11):

GAA TTC CAG CCT TCA GGT GAA CAT GGC TCC GGT GAA CAG CCT TCT
GGT GAG CAG GCC TCG GGT GAA CAG CCT TAG,

Oligo SP 2 (SEQ ID NO: 12):

GTG AGC ACG CTT CAG GGG AAC AGC CTT CAG GTG CAC CAA TTT CAA
GCA CAT CTA CAG GCA CAA TAT TAA ATT GCT,

Oligo SP 3 (SEQ ID NO: 13):

ACA CAT GTG CTT ATA TGA ATG ATC AAG GAA AAT GTC TTC GTG GAG
AGG GAA CCT GCA TCA CTC AGA ATT C,

Oligo SP 3a(3Cys-> Ala) (SEQ ID NO: 14):

ACA CAG CAG CTT ATA TGA ATG ATC AAG GAA AAG CAC TTC GTG GAG
AGG GAA CCG CAA TCA CTC AGA ATT C,

Oligo SP 4 (SEQ ID NO: 15):

GAA TTC TGA GTG ATG CAG GTT CCC TCT CCA CGA AGA CAT TTT CCT
TGA TCA TTC ATA TAA GCA CAT GTG TAG CAA TTT A,

Oligo SP 4a (3Cys->Ala) (SEQ ID NO: 16):

GAA TTC TGA GTG ATT GCG GTT CCC TCT CCA CGA AGT GCT TTT TGA
TGA TCA TTC ATA TAA GCT GCT GTG TAG CAA TTT A,

Oligo SP 5 (SEQ ID NO: 17):

ATA TTG TGC CTG TAG ATG TGC TTG AAA TTG GTG CAC CTG AAG CCT
GTT CCC CTG AAG CGT GCT CAC CTG AAG GCT,

Oligo SP 6 (SEQ ID NO: 18):

GTT CTC CCG AGG CCT GCT CAC CAG AAG GCT GTT CAC CGG AGC CAT
GTT CAC CTG AAG GCT GGA ATT C--

B11
Cont.

Beginning on page 42, at line 25, continuing to page 43, line 17, please amend
the paragraph beginning "Practically, the first two amino acid codons" as follows:

--Practically, the first two amino acid codons of the sperm cell specific
epitope, MSA-63, an oligonucleotide encoding residues 143 and 144 (i.e. GTC GGC,
infra), is cloned into the immunoglobulin CDR, using the methods described *infra*.

The MSA-63 DNA sequence encoding the epitope:

GTC GGC AGC CTC CGA AGC AGC CCG CTC CAG AGC CCG CTG CTC CGA
CCG CTC GTC CAG AGC AGC CTC TGC TTG CTG TTC CTC TTG CTG CGA
TAC AGC TGC GGC GAC GGC AGC TGC AGC CGA CGA TAC TGC GAC TTG
ACG GTG TGC CGG CGA ATG TAC TTG CTG CTG CGA TTC ACG GAC CCG
CCG CTC CCG CAG ACG TGC TGC GTC TTG AGC (SEQ ID NO: 19)

B12

The MSA-63 protein sequence epitope encoded by the nucleic acid sequence above,
which starts at amino acid 143 and ends at 233.

Gln Pro Ser Glu Ala Ser Ser Gly Glu Val Ser Gly Asp Glu Ala Gly Glu Gln Val Ser
Ser Glu Thr Asn Asp Lys Glu Asn Asp Ala Met Ser Thr Pro Leu Pro Ser Thr Ser Ala
Ala Ile Thr Leu Asn Cys His Thr Cys Ala Tyr Met Asn Asp Asp Ala Lys Cys Leu Arg
Gly Glu Gly Val Cys Thr Thr Gln Asn Ser (SEQ ID NO: 20)

For the second two amino acid codons, an oligonucleotide encoding residues 144 and
145 is utilized (*i.e.*, GGC AGC). For the third, 145 and 146 and so on until the entire
epitope is synthesized and inserted into the CDR, two amino acids at a time. For
peptides three amino acids in length, an oligonucleotide encoding residues 143 to 146

is synthesized. The second oligonucleotide synthesized encodes residues 146 to 148. The third encodes residues 148 to 150, and this continues until the entire epitope is covered in this fashion. The next oligonucleotide that is synthesized is four amino acid codons in length. It begins with residues 143 to 146, its second segment is equivalent to residues 145 to 148, its third segment corresponds to residues 147 to 150, and so on until the entire epitope is transitioned in this fashion. The next oligonucleotide synthesized contains five amino acid codons with two overlapping with the previous. For example, the first oligonucleotide encodes residues 143 to 147, and the second residues 146 to 150. This pattern continues until the entire epitope has been transitioned. The next construct encoding an epitope uses nucleotides for six amino acid codons with two overlapping with the previous codons as described *infra*--

B12
CONT.

On page 43, at line 24, please amend the paragraph beginning "In a specific example," as follows:

--In a specific example, oligomers have been designed which scan the entire length of the MSA-63 epitope and encode 15 amino acids. Each oligo overlaps with the previous one for the equivalent of five amino acids. MSA-63 oligos encoding 15 amino acids, with overlap of five amino acids each:

MSA1: GTC GGC AGC CTC CGA AGC AGC CCG CTC CAG AGC CCG CTG CTC CGA (SEQ ID NO: 21)

MSA2: AGC CCG CTG CTC CGA CCG CTC GTC CAG AGC AGC CTC TGC TTG CTG (SEQ ID NO: 22)

MSA3: AGC CTC TGC TTG CTG TTC CTC TTG CTG CGA TAC AGC TGC GGC GAC (SEQ ID NO: 23)

MSA4: TAC AGC TGC GGC GAC GGC AGC TGC AGC CGA CGA TAC TGC GAC TTG (SEQ ID NO: 24)

MSA5: CGA TAC TGC GAC TTG ACG GTG TGC ACG CGA ATG TAC TTG CTG CTG (SEQ ID NO: 25)

MSA6: ATG TAC TTG CTG CTG CGA TTC ACG GAC GCG CCG CTC CCG CAG ACG (SEQ ID NO: 26)

B13
CONT.

MSA7: CGA TTC ACG GAC GCG CCG CTC CCG CAG ACG TGC TGC GTC
TTG AGC (SEQ ID NO: 27)--

On page 44, at line 1, please amend the paragraph beginning "Antibodies in which a portion" as follows:

--Antibodies in which a portion of the MSA-63 antigen has been inserted into CDR1, *i.e.*, where residues Lys24 through Ala34 of the consensus contraceptive light chain, the sequence of which is in Figure 15, are replaced with the sequence Gln-Pro-Ser-Glu-Ala-Ser-Ser-Gly-Glu-Val-Ser-Gly-Asp-Glu-Ala-Gly-Glu (SEQ ID NO: 28). The antibody, MSA1, can be constructed using the oligonucleotides provided in Figure 11 in the scheme provided in Figure 8 and described below, where the identities of oligonucleotides 1-12 are indicated in Table 7. The antibody MSA1VAC can also be constructed using the oligos of Figure 11 by the scheme of Figure 8, as indicated in Table 7. MSA1VAC is the same as MSA1 except that the cysteine at position 23 of the light chain variable region has been replaced with alanine. These light chains can be expressed with the heavy chain consensus sequence CONVH1, the sequence of which is provided in Figure 7B, and the construction of which can be accomplished with the oligonucleotides as indicated in Table 4. These single stranded oligonucleotides sequences are annealed to create cohesive double stranded DNA fragments suitable for ligation as diagramed in Figure 8, along with oligonucleotides encoding the remainder of the consensus variable region, to construct the variable region gene. For the MSA-63 containing variable regions MSA1 and MSA1VAC the oligonucleotides corresponding to oligonucleotides 1 to 10, or 1 to 12, of Figure 8 are provided in Table 7, and the sequences of these oligonucleotides are provided in Figure 11. Specifically, oligonucleotides of about 70 bases in length corresponding to the sequences of interest with 20 base overlapping regions are synthesized (GenoSys Biotech Inc.). Each oligonucleotide is 5' phosphorylated as follows: 25 μ l of each oligo is incubated for one hour in the presence of T₄ polynucleotide kinase and 50 mM ATP in appropriate buffer at 37°C. The enzyme is heat killed and the reaction stopped by heating for ten minutes at 70°C followed by ethanol precipitation with sodium acetate. The oligos are then resuspended in TE buffer (10 mM Tris, pH 8.0, 1 mM EDTA).--

B14